REMARKS

Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections for at least the following reasons. Claims 22 and 32 have been amended to more accurately recite the subject matter of the present application. Claims 49, 52, 55, 57 and 58 have been amended to place the claims in better condition for examination. Claims 40 and 41 have been amended to depend upon claim 32. No new matter has been added.

Claims 49, 52, 55, 57 and 58 stand rejected under 35 U.S.C. § 112, second paragraph. Applicants submit that the amendments to these claims to place these claims in condition to satisfy the requirements of 35 U.S.C. § 112, second paragraph. These claims now recite tumors associated with hyper methylation and tumors associated with gene silencing.

Claims 22-24, 28, 29, 32, 39, 42-44 and 47 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Greer (WO 85/01871). Applicants respectfully submit that Greer does not and can not anticipate the present claims for at least the following reasons.

The Examiner contends, at page 5 of the outstanding Office Action, that Greer anticipates the previous claims of record because Greer discloses administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient followed by an effective level of radiation, regardless of whether or not a pre-treatment with N-(Phosphonacetyl)-L-Aspartate (PALA), 5-Fluoro-2'-deoxycytidine (FdC), 4-N-methyl 5-Fluoro-2'-deoxycytidine (4-N-methyl FdC) or 5-Fluoro-2'-deoxyuridine (FdU) is administered to the

patient. Applicants understand the Examiner's interpretation of the previous claims of record and have amended the present claims as a way of more accurately reciting the nature of the subject matter of the present invention.

As described in the Rule 1.132 Declaration of Dr. Sheldon Greer, filed February 26, 2007, those of skill in the art would not have believed that administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine without a pre-treatment with N-(Phosphonacetyl)-L-Aspartate (PALA), 5-Fluoro-2'-deoxycytidine (FdC), 4-N-methyl 5-Fluoro-2'-deoxycytidine (4-N-methyl FdC) or 5-Fluoro-2'-deoxyuridine (FdU), followed by radiation treatment, would have been a successful method of tumor treatment.

The Examiner's contends, at page 3 of the outstanding Office Action, that exposing a tumor to radiation would result in treatment of the tumor to some degree, whether or not 5-chloro-2'-deoxycytidine and tetrahydrouridine are administered prior to the radiation. The Examiner further contends, at page 5 of the outstanding Office Action, that "a method of treating a tumor with radiation does not require any type of chemical treatment prior to radiation. Radiation is generally effective to kill both cancerous and non-cancerous cells." Applicants submit that while this may be true, to be effective in killing cancer cells, the radiation levels required for such killing would need to be administered in high doses. One of skill in the art would appreciate that a tumor may be treated with radiation alone, and the tumor may respond to such treatment. However, such required high dosages would be too toxic and aggressive for the patient to handle, and could very likely lead to the death of the patient. One of skill in the art would also

appreciate that even with high dose radiation treatment alone, there is no guarantee of effective tumor control.

Applicants submit that the Examiner has relied upon the preamble of the previous claims of record as support for this outstanding rejection. As such, Applicants have amended the preamble to more accurately recite the subject matter of the present application. Applicants respectfully request the Examiner to consider the current preamble in a similar manner. In other words, if the preamble in the previous claims of record were used as a basis for rejection, the current preamble must be given the same weight.

Applicants have amended the current preamble to present claims 22 to recite "A method of achieving tumor control and improved radiation efficacy in at least one human tumor in a patient in need of such tumor control." Claim 32 has been similarly amended. Applicants submit that one of skill in the art would recognize that tumor control is taken to mean tumor remission or tumor growth delay. Applicants also submit that one of skill in the art would recognize that improved radiation efficacy means a level of radiation that is effective in tumor remission/tumor growth delay with reduced toxic side effects conferred to the patient undergoing such treatment.

In previous mouse tumor models, such as those described in Greer, sensitization by chemical treatment prior to radiation did not equate to good therapeutic efficacy and did not translate to effective tumor control. It was thought necessary to lower competing nucleoside pools in order to reach adequate levels of CldUMP in tumors. One of skill in the art may achieve some level of sensitization, but in order to get tumor remission or

tumor growth delay, one needs to have a sufficient amount of CldUMP and CldU incorporated into the tumor. It was an unexpected finding of the present application that CldC + H_4U alone at higher doses could result in effective amounts of CldUMP and CldU in tumors without the need for modulation. The findings that CldUMP inhibits thymidylate synthetase (TS) and that CldUMP may inhibit diphosphate reductase further enhances its incorporation into the tumor. This feature helps explain the therapeutic benefit achieved with methods described in the present claims. This feature was not known before the filing of this application.

Applicants would like to emphasize that an important and unexpected feature of CldUMP formed from CldC is that CldUMP can inhibit (TS), an important source of the normal metabolite TTP (which competes with CldUTP for incorporation into DNA). Therefore, CldC in high concentrations will not only over run the cellular pools of TTP, but will inhibit their formation. This is thought to account for the omission of FdC and PALA in the methods described by the present claims without a loss of efficacy of CldC plus H_4U. FdC and PALA in the protocol of Greer mainly function by lowering the pools of TTP, thereby facilitating incorporation of CldUMP and CldU in tumors.

Accordingly, Applicants respectfully submit that the methods described in the present claims provide a clear technical advantage and improvement over the methods described by Greer. For at least the above reasons, Applicants submit that methods described in the present claims are novel and can not be anticipated by Greer.

Claims 30, 31, 40 and 41 stand rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871) in view of Shepherd (*Cancer*, 1992, v. 70, 2250-

2254). Applicants respectfully submit that the combination of Greer and Shepherd does not and can not render obvious the present claims.

Claims 30, 31, 40 and 41 are dependent, directly or indirectly, from either of claims 22 or 32. As argued above, it was an unexpected finding that the methods described in present claims 22 and 32 would provide a technical advantage over methods described in Greer. Accordingly, Applicants submit that one of skill in the art would not have relied upon Greer to arrive at methods described in present claims 22 and 32. Since Shepherd is only relied upon to teach the use of yttrium 90 as source of radiation, Shepherd does not cure the noted deficiencies of Greer. Thus, the combination of Greer and Shepherd can not render obvious claims 30, 31, 40 and 41.

Claims 33, 45, 46, 48, 50, 51, 53-56, 58 and 59 stand rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871). Applicants respectfully submit that Greer can not render obvious the present claims.

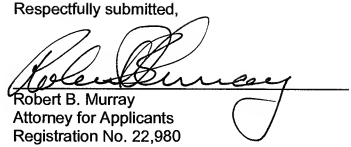
Claims 33, 45, 46, 48, 50, 51, 53-56, 58 and 59 are dependent, directly or indirectly, from either of claims 22 or 32. As argued above, it was an unexpected finding that the methods described in present claims 22 and 32 would provide a technical advantage over methods described in Greer. Accordingly, Applicants submit that one of skill in the art would not have relied upon Greer to arrive at methods described in present claims 22 and 32 to treat patients having cancers of the breast, lung, brain, liver, kidney, ovaries, uterus, testis, pancreas, gastrointestinal tract, head and neck, nasopharynx, skin and prostate.

Claims 49, 52 and 57 stand rejected under 35 U.S.C. § 103(a) as being obvious over Greer (WO 85/01871) in view of Nagatake (Cancer Research, 1996, v. 56, 1886-1891). Applicants respectfully submit that the combination of Greer and Nagatake does not and can not render obvious the present claims.

Claims 49, 52 and 57 are dependent, directly or indirectly, from either of claims 22 or 32. As argued above, it was an unexpected finding that the methods described in present claims 22 and 32 would provide a technical advantage over methods described in Greer. Accordingly, Applicants submit that one of skill in the art would not have relied upon Greer to arrive at methods described in present claims 22 and 32. Since Nagatake is only relied upon to teach the treatment of tumors associated with hypermethylation, Nagatake does not cure the noted deficiencies of Greer. Thus, the combination of Greer and Nagatake can not render obvious claims 49, 52 and 57.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the outstanding Office Action rejections. Early and favorable action is awaited. The Director is authorized to charge any fees or overpayment to Deposit Account No. 02-2135.

Respectfully submitted,

By 

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